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SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/210,902	03/21/94	NABEL	VICAL.035A

E

EXAMINER
NEWELL, W

ART UNIT	PAPER NUMBER
1804	8

DATE MAILED: 08/07/95

18M2/0807

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 2/13/95 ☒ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), ____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-12, 14, 15 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☒ Claims 13, 16-20 have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☒ Claims 1-12, 14, 15 are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).

12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.

13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

EXAMINER'S ACTION

This Action is responsive to Applicant's amendment dated February 10, 1995. The amendments to claims 1, 7, 12 and 14 are acknowledged. The cancellation of claims 13 and 16-20 by the Applicant is acknowledged. Claims 1-12, 14 and 15 remain presented for examination.

The rejection of claims 1-20 under 35 U.S.C. § 101 is withdrawn in light of the GUIDELINES FOR EXAMINATION OF APPLICATIONS FOR COMPLIANCE WITH THE UTILITY REQUIREMENT.

Discussion of Rejections Under 35 U.S.C. § 112

The requirement under 35 U.S.C. § 112 for deposit of the Ad.HSV-tk vector disclosed in the specification is maintained. Given the guidance of the specification it is unlikely that one of ordinary skill in the art would obtain vector of the precise sequence as the Applicant's vector; the expression level of the tk gene in transduced cells might therefore vary, increasing the unpredictability of using the invention as claimed.

The rejection of claims 1-20 under 35 U.S.C. § 112, first paragraph, for failing to provide an enabling disclosure and an adequate written description of the invention is maintained. Applicant's arguments filed March 21, 1994 have been fully considered but they are not deemed to be persuasive. The rejection under 35 U.S.C. § 112, first paragraph, is not based upon "whether an invention is operable, or useful, as broadly as it is claimed", as maintained by the Applicant (Amendment, page

3). Rather, the Applicant is required to provide sufficient guidance to enable one of ordinary skill in the art at the time the invention was made to make and use the invention without undue experimentation. The specification fails to meet the requirement of 35 U.S.C. § 112, first paragraph, in this regard.

Applicants state that they "do not claim human gene therapy per se" (Amendment, page 6). The invention is broadly directed to the delivery of nucleic acids to the cells of a blood vessel in a mammal, for the therapeutic purpose of inhibiting vascular smooth muscle cell proliferation. It is clear that a primary embodiment of the invention is the treatment of restenosis in human beings following mechanical treatment of balloon angioplasty, laser, atherectomy device, or stent. As such, the invention must be enabled for this purpose; that is, sufficient guidance must be presented to enable a skilled artisan to treat any and all mechanical treatments of blood vessels in any and all mammals, including humans. It is maintained that the specification has failed to meet this requirement.

The argument (Amendment, Nabel declaration pages 2-3, Exhibits A-F) that the pig model presented in the specification is sufficient to predict the successful use of the invention in other animals, especially humans, is not found to be persuasive. Applicant maintains that "the pig model is the most correlatable predictor of human efficacy in treatments involving inhibition of restenosis". The Lee reference was cited in the first Office

Action as evidence of the significant differences in gene transfer to the arterial wall between species. The Ohno reference, cited by Applicants (Amendment, Exhibit D) does note the similarities between the pig model and human vascular proliferative disease (page 781, column 1); it further notes that

"although the efficacy of ADV-tk gene transfer for balloon injury in this porcine model may provide a more relevant test than the injured rat carotid artery for its appropriateness in humans, the model still differs from human restenosis in that these pigs are not hyperlipidemic. It is known that gene transfer can be achieved in atherosclerotic rabbit arteries; however it remains to be determined whether this approach will prove therapeutic for humans" (page 783, column 3).

The Schwartz reference (Exhibit A), while noting the similarity of the pig model to the proliferative component of human restenosis, also notes that "efforts to reduce or eliminate restenosis after PTCA have largely been unsuccessful", due to "a lack of knowledge regarding the pathophysiolgical mechanisms of human restenosis and the lack of an accurate animal restenosis model with substantial proliferation" (Schwartz, page 2193). This statement provides evidence of additional factors specific to restenosis in humans that the porcine model is not able to address. Such species differences may increase the unpredictability of using the invention in human beings; the specification provides no guidance to one skilled in the art to account for these factors. Ferrell et al. (exhibit B) notes that "research conducted in the pig and primate appears to be the most predictive of results in humans", the authors further note that "given the complex biology of restenosis and the multiple

influences that are active, including injury, thrombosis, cellular proliferation, growth factors, coronary spasm, and cellular recoil, it is unlikely that a single intervention will be effective in limiting restenosis in humans" (Ferrell, page 1631). The evidence of long-term effectiveness for the invention in the porcine model (Ohno reference, August 1994), as well as the accumulated results of animal studies using the invention, are not contained in the specification, and were not known to one of ordinary skill in the art at the time the invention was made. The results of Exhibits E and F, in which the studies described in the specification have been extended to a larger number of animals, were obtained after the time the invention was made, are not contained in the specification, and thus could not guide one of ordinary skill in the art at the time the invention was made to make and use the claimed invention. In light of the evidence of significant species differences, and in the absence of information in the specification that would lead one of ordinary skill in the art to account for these differences, the rejection under 35 U.S.C. § 112, first paragraph, on these grounds is maintained.

Applicant contends that "the antisense approach of Morishita et al. is irrelevant to Applicants' adenovirus approach" (Amendment, page 7). The invention as claimed however, is not limited to adenoviral vector delivery of nucleic acid to cells. Claim 1 is directed to "introducing a polynucleotide to said

blood vessel after said mechanical treatment"; the delivery system is not specified. Only Claim 5 and claims that depend on claim 5 are limited to adenoviral vectors. Thus sufficient guidance to make and use the invention to therapeutic effect must be presented for all viral vectors (retroviral, adenoviral, etc.) as well as non-viral delivery methods. It is admitted that differences exist between the antisense approach of Morishita and the approaches claimed by the Applicant. However, the difficulties based on "the complexity of neointima formation and/or the inability to deliver sufficient quantities of drugs to the site of injury" (Morishita page 8474, column 1) remain pertinent to the claimed invention. The specification provides no working example, and insufficient guidance, to enable use of non-viral vectors such as liposomes. The argument that "current second and third generation cationic liposomes" (Amendment, page 9) provide sufficient gene transfer in vivo to produce a therapeutic effect is not supported by the specification. The only liposome formulation disclosed in the specification is Lipofectin (TM, Gibco/BRL)(Specification, page 7, lines 9-10).

The first Office Action maintained that delivery of vector at the time of mechanical injury might be insufficient to transduce enough cells to achieve the results of the exemplified adenoviral vector. Applicant responded that the claims "do not recite that the method must be the most efficient". While this is true, the claimed invention must achieve the therapeutic

inhibition of restenosis; thus efficient gene transfer is essential for one of ordinary skill to use the invention. It was further argued that transfection days after arterial denudation (rather than simultaneously with catheterization) is contemplated by the language of the claims. Even if the claims encompass such an application, the specification must provide specific guidance to the skilled artisan to use the invention in this manner.

Applicant argues that the specification presented is enabling for any and all mechanical means of injury. The Santoian reference provides evidence that different mechanical injuries induce different patterns of vascular proliferation. In light of the complex, multifactorial nature of the proliferation process, and the lack of guidance provided to specifically address each form of injury, it is still maintained that the specification is not enabling to treat any and all mechanical means of injury with the invention with a reasonable expectation of success.

Rejections of Claims 1, 4, 7, 12, 14 and 16 made under 35 U.S.C. § 112, second paragraph, are withdrawn in light of the submission of amended claims.

Discussion of Rejections Under 35 U.S.C. § 103

The rejection of Claims 1,2, and 12-15 as unpatentable over Takeshita et al. in view of Plautz et al. is maintained. Applicant argues (Amendment, pages 12-13; Nabel declaration,

pages 5-6) that reduction in stenosis after PTA is not a result of transfer of the luciferase gene to the arterial wall, and is not the same as a reduction in restenosis. Takeshita discloses in vivo transfer of genes to blood vessels, notes a decrease in percent diameter of stenosis, and further identifies "adjunctive gene transfer post-PTA as a potential strategy to reduce restenosis". Takeshita uses liposomes to transfer genes to cells in the arterial wall that are proliferating as a result of PTA-caused injury. It is clear that Takeshita is employing the same general method, of in vivo gene transfer, for the same general purpose, inhibition of restenosis. The difference between the disclosure of Takeshita and the claimed invention is the use of the HSV-tk gene by the applicant. The Plautz reference teaches "a method to eliminate cells undergoing rapid growth in vivo" by transfer of the HSV-tk gene (abstract), and even suggests its usefulness in cardiovascular applications (introduction). In that the smooth muscle cells involved in restenosis are certainly undergoing rapid growth in vivo, the Plautz reference is analogous art. It would have been obvious to one of ordinary skill in the art at the time the invention was made to transfer genes in vivo to arterial wall smooth muscle cells as a potential restenosis treatment as taught by Takeshita, and to employ gene transfer of the HSV-tk gene in particular in light of the teaching of Plautz that HSV-tk gene transfer followed by

ganciclovir treatment is effective in limiting the growth of proliferating cells.

As the other rejections under 35 U.S.C. § 103 are based on the same argument as above, that the combination of Takeshita and Plautz references is insufficient grounds for an obviousness rejection, the Examiner's arguments are maintained.

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Newell whose telephone number is (703) 308-7307. The examiner can normally be reached on Monday to Friday from 8:30 AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jacqueline Stone, can be reached on (703) 308-3153 . The fax phone number for this Group is (703)308-0294 .

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703)308-0196 .

Michael Newell

June 22, 1995

SUZANNE E. ZISKA
PRIMARY EXAMINER
GROUP 1800